

AMENDMENTS TO THE SPECIFICATION

Please replace the following paragraphs as amended:

[0220] Mouse hybridoma line Myc 1-9E10.2 expresses a murine monoclonal antibody (IgG1) that recognizes a human c-myc epitope of amino acid sequence EQKLISEEDL Seq ID NO: 123 (G. I Evans et al., Molec. Cell. Biol. 5: 3610-3616, 1985). Cells were obtained from ATCC (CRL-1729) and cultured under standard conditions. 2×10^6 cultured cells were spun and washed to remove excess culture media and lysed with 600 μ L RLT buffer containing 1% 2-mercaptoethanol (Qiagen, Valencia, Calif.). Total RNA was purified using the QIAshredder and ~~RNEASY~~ RNeasy column per manufacturers directions. Briefly, the cell lysate was applied to the QIAshredder column and spun in a centrifuge for 2 minutes at 14K rpm. The flow through was collected and diluted with an equal volume of 70% ethanol. The mixture was transferred to an RNeasy column and centrifuged for 15 seconds at 10K rpm until all sample was processed through the column. The RNA bound to the column was washed with 700 μ L RW1 followed by a wash with 500 μ L RPE and subsequently dried. The purified RNA was eluted in 50 μ L RNASE free water by centrifugation for 1 minute at 10K rpm. First strand cDNA was synthesized from 0.8 μ g total RNA using a SMART 3' RACE kit (BD Biosciences Clontech, Palo Alto, Calif.) with 1 μ L 3' CDS primer in 5 μ L. The RNA primer mix was heated to 70°C for 2 minutes and placed on ice for an additional 2 minutes. To the RNA and primer mix was brought to 10 μ L containing 1X First strand buffer, 2 mM DTT, 1 mM dATP, 1 mM dCTP, 1 mM dGTP, 1 mM dTTP and 1 μ L Powerscript Reverse Transcriptase. The reaction was incubated at 42°C for 90 minutes and then 100 μ L of Tricine-EDTA Buffer (10 mM Tricine-KOH, pH 8.5, 1 mM EDTA) was added and the reaction heated to 72°C for 7 minutes. The 9E10 kappa light chain was PCR amplified in a 50 μ L [L] reaction containing 1X Advantage 2 PCR Buffer, 0.2 mM dATP, 0.2 mM dCTP, 0.2 mM dGTP, 0.2 mM dTTP, 1X Advantage 2 Polymerase Mix, 2.5 μ L of prepared cDNA, 1X UPM, and 0.2 μ M 9E10k15' (Seq ID No: 50). The 9E10k15' primer was designed to anneal to the murine kappa light leader sequence from germline sequence V-21C9.5KB'CL. The reaction was cycled 5 times at 94°C for 5 seconds, 72°C

for 3 minutes followed by 5 times at 94°C for 5 seconds, 70°C for 10 seconds, 72°C for 3 minutes and 25 cycles at 94°C for 5 seconds, 67°C for 10 seconds, 72°C for 3 minutes. The amplification of the desired approximately 900 bp fragment was confirmed by agarose gel electrophoresis. The 9E10 heavy chain was PCR amplified in a 50 μ L [L] reaction containing 1X Advantage 2 PCR Buffer, 0.2 mM dATP, 0.2 mM dCTP, 0.2 mM dGTP, 0.2 mM dTTP, 1X Advantage 2 Polymerase Mix, 2.5 μ L of prepared cDNA, 1X UPM, and 0.4 μ M 9E10gfw5' (Seq ID No: 51). The 9E10gfw5' primer was designed to anneal to the murine heavy chain variable FR1 sequence identified from germline sequence Vh7183(Vh69.1). The reaction was cycled 5 times at 94°C for 5 seconds, 70°C for 3 minutes followed by 5 times at 94°C for 5 seconds, 68°C for 10 seconds, 72°C for 3 minutes and 25 cycles at 94°C for 5 seconds, 64°C for 10 seconds, 72°C for 3 minutes. The amplification of the desired approximately 1.6 Kb fragment was confirmed by agarose gel electrophoresis.

Between paragraphs 328 and 329, replace ~~Conclusions~~ with Further Examples

[0329] The following EXAMPLES are representative of the structures and methods represented by this invention.

[0330] EXAMPLE 26 [[1.]] An artificial preproprotein, comprising four peptide sequences a signal peptide sequence; a first peptide sequence of interest attached to the c-terminus of the signal peptide sequence; a propeptide sequence attached to the c-terminus of the first peptide sequence of interest; and a second peptide of interest attached to the c-terminus of the propeptide sequence wherein the propeptide sequence is not naturally associated with either the first or the second peptide of interest.

[0331] EXAMPLE 27 [[2.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody, but the first peptide is different from the second peptide.

[0332] EXAMPLE 28 [[3.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody.

[0333] EXAMPLE 29 [[4.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 28 [[3]] wherein the first peptide and the second peptide are both heavy chain peptides.

[0334] EXAMPLE 30 [[5.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 28 [[3]] wherein the first peptide is a light chain of the antibody.

[0335] EXAMPLE 31 [[6.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises a Fab fragment light chain peptide and an Fab fragment heavy chain peptide, wherein the first peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the second peptide is either a heavy

chain of the Fab fragment or a light chain of the Fab fragment, but the first peptide, but the first peptide is different from the second peptide.

- [0336] EXAMPLE 32 [[7.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises a Fab fragment light chain peptide and an Fab fragment heavy chain peptide, wherein the first peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the second peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment.
- [0337] EXAMPLE 33 [[8.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 32 [[7]] wherein the first peptide and the second peptide are both heavy chain peptides.
- [0338] EXAMPLE 34 [[9.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 32 [[7]] wherein the first peptide and the second peptide are both light chain peptides.
- [0339] EXAMPLE 35 [[10.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the first peptide is either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative, and wherein the second peptide is either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative but the first peptide is different from the second peptide.
- [0340] EXAMPLE 36 [[11.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]] that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the first peptide is either a heavy chain of the Fab fragment or antibody derivative or a light chain of the Fab fragment or antibody derivative, and wherein the second peptide is either a heavy chain of the Fab fragment or antibody derivative or a light chain of the Fab fragment or antibody derivative.
- [0341] EXAMPLE 37 [[12.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 36 [[11]] wherein the first peptide and the second peptide are both heavy chain peptides.
- [0342] EXAMPLE 38 [[13.]] The artificial preproprotein of ~~conclusion~~ EXAMPLE 36 [[11]] wherein the first peptide and the second peptide are both light chain peptides.

[0343] EXAMPLE 39 [[14.]] An artificial polynucleotide, comprising four nucleotide sequences: a first nucleotide sequence that encodes a signal peptide sequence; a second nucleotide sequence that encodes a first peptide of interest, second nucleotide sequence being connected to the 3' terminus of the first nucleotide sequence; a third nucleotide sequence that encodes a propeptide, third nucleotide sequence being connected to the 3' terminus of the second nucleotide sequence; and a fourth nucleotide sequence that encodes a second peptide of interest, fourth nucleotide sequence being connected to the 3' terminus of the third nucleotide sequence.

[0344] EXAMPLE 40 [[15.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody, but the first peptide is different from the second peptide.

[0345] EXAMPLE 41 [[16.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody.

[0346] EXAMPLE 42 [[17.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE [[16]] wherein the first peptide and the second peptide are both heavy chain peptides.

[0347] EXAMPLE 43 [[18.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 41 [[16]] wherein the first peptide is a light chain of the antibody.

[0348] EXAMPLE 44 [[19.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises a Fab fragment light chain peptide and an Fab fragment heavy chain peptide, wherein the first peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the second peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment, but the first peptide, but the first peptide is different from the second peptide.

- [0349] EXAMPLE 45 [[20.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises a Fab fragment light chain peptide and an Fab fragment heavy chain peptide, wherein the first peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the second peptide is either a heavy chain of the Fab fragment or a light chain of the Fab fragment.
- [0350] EXAMPLE 46 [[21.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 45 [[20]] wherein the first peptide and the second peptide are both heavy chain peptides.
- [0351] EXAMPLE 47 [[22.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 45 [[20]] wherein the first peptide and the second peptide are both light chain peptides.
- [0352] EXAMPLE 48 [[23.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the first peptide is either a heavy chain of the Fab fragment derivative or antibody derivative or a light chain of the Fab fragment or antibody derivative, and wherein the second peptide is either a heavy chain of the Fab fragment or antibody derivative or a light chain of the Fab fragment or antibody derivative but the first peptide is different from the second peptide.
- [0353] EXAMPLE 49 [[24.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] that encodes a polypeptide that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the first peptide is either a heavy chain of the Fab fragment derivative or antibody derivative or a light chain of the Fab fragment or antibody derivative.
- [0354] EXAMPLE 50 [[25.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 49 [[24]] wherein the first peptide and the second peptide are both heavy chain peptides.
- [0355] EXAMPLE 51 [[26.]] The artificial polynucleotide of ~~conclusion~~ EXAMPLE 49 [[24]] wherein the first peptide and the second peptide are both light chain peptides.
- [0356] EXAMPLE 52 [[27.]] A method of making an artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]], comprising: providing a first, a second, a third and a fourth nucleotide sequence that encode a signal peptide sequence, a first peptide of interest, a propeptide and a second peptide of interest respectively; connecting the 3'

terminus of the first nucleotide sequence to the 5' terminus of the second nucleotide sequence; connecting the 3' terminus of the second nucleotide sequence to the 5' terminus of the third nucleotide sequence; and connecting the 3' terminus of the third nucleotide sequence to the 5' terminus of the fourth nucleotide sequence, wherein the nucleotide sequence that encodes a first peptide of interest can be the same as or different from the nucleotide sequence that encodes a second peptide of interest.

[0357] EXAMPLE 53 [[28.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the second nucleotide sequence encodes either a heavy chain of the antibody or a light chain of the antibody, and wherein the fourth nucleotide sequence encodes either a heavy chain of the antibody or a light chain of the antibody, but the second nucleotide sequence is different from the fourth nucleotide sequence.

[0358] EXAMPLE 54 [[29.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the second nucleotide sequence encodes either a heavy chain of the antibody or a light chain of the antibody, and wherein the fourth nucleotide sequence encodes either a heavy chain of the antibody or a light chain of the antibody.

[0359] EXAMPLE 55 [[30.]] The method of ~~conclusion~~ EXAMPLE 54 [[29]] wherein the second nucleotide sequence and the fourth nucleotide sequence both encode a heavy chain polypeptide.

[0360] EXAMPLE 56 [[31.]] The method of ~~conclusion~~ EXAMPLE 54 [[29]] wherein the second nucleotide sequence and the fourth nucleotide sequence both encode a light chain polypeptide.

[0361] EXAMPLE 57 [[32.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises a Fab light chain peptide and an antibody heavy chain peptide, wherein the second nucleotide sequence encodes either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the fourth nucleotide sequence encodes either a heavy chain of the Fab

fragment or a light chain of the Fab fragment, but the second nucleotide sequence is different from the fourth nucleotide sequence.

[0362] EXAMPLE 58 [[33.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises a Fab light chain peptide and an antibody heavy chain peptide, wherein the second nucleotide sequence encodes either a heavy chain of the Fab fragment or a light chain of the Fab fragment, and wherein the fourth nucleotide sequence encodes either a heavy chain of the Fab fragment or a light chain of the Fab fragment.

[0363] EXAMPLE 59 [[34.]] The method of ~~conclusion~~ EXAMPLE 58 [[33]] wherein the second nucleotide sequence and the fourth nucleotide sequence both encode a heavy chain polypeptide.

[0364] EXAMPLE 60 [[35.]] The method of ~~conclusion~~ EXAMPLE 58 [[33]] wherein the second nucleotide sequence and the fourth nucleotide sequence both encode a light chain polypeptide.

[0365] EXAMPLE 61 [[36.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the second nucleotide sequence encodes either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative, and wherein the fourth nucleotide sequence encodes either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative but the second nucleotide sequence is different from the fourth nucleotide sequence.

[0366] EXAMPLE 62 [[37.]] The method of ~~conclusion~~ EXAMPLE 52 [[27]] wherein the artificial polynucleotide encodes a polypeptide that comprises a light chain peptide and a heavy chain peptide of a Fab fragment derivative or an antibody derivative, wherein the second nucleotide sequence encodes either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative, and wherein the fourth nucleotide sequence encodes either a heavy chain of the Fab fragment or Antibody derivative or a light chain of the Fab fragment or Antibody derivative.

[0367] EXAMPLE 63 [[38]], The method of ~~conclusion~~ EXAMPLE 62 [[37]] wherein the second nucleotide sequence and the fourth nucleotide sequence both are derived from a nucleotide sequence that encodes a heavy chain peptide.

[0368] EXAMPLE 64 [[39.]] The method of ~~conclusion~~ EXAMPLE 62 [[37]] wherein the second nucleotide sequence and the fourth nucleotide sequence both are derived from a nucleotide sequence that encodes a light chain peptide.

[0369] EXAMPLE 65 [[40.]] A method of making an artificial preproprotein, comprising: making an artificial polynucleotide that encodes the preproprotein; and expressing the artificial polynucleotide in a host organism whereby the preproprotein is made.

[0370] EXAMPLE 66 [[41.]] A method of making a multimeric protein, comprising: providing a first, a second, a third and a fourth nucleotide sequence that encode a signal peptide sequence, a first peptide of interest, a propeptide and a second peptide of interest respectively; connecting the 3' terminus of the first nucleotide sequence to the 5' terminus of the second nucleotide sequence; connecting the 3' terminus of the second nucleotide sequence to the 5' terminus of the third nucleotide sequence; and connecting the 3' terminus of the third nucleotide sequence to the 5' terminus of the fourth nucleotide sequence, so that an artificial polynucleotide results and is comprised of the four nucleotide sequences, and wherein the nucleotide sequence that encodes a first peptide of interest can be the same as or different from the nucleotide sequence that encodes a second peptide of interest; introducing the resulting artificial polynucleotide into a host organism by transfection, or by stable transformation; allowing the artificial polynucleotide to be expressed in the host organism whereby a preproprotein is made; allowing the preproprotein to be processed into a mature polypeptide.

[0371] EXAMPLE 67 [[42.]] The method of ~~conclusion~~ EXAMPLE 66 [[41]] further comprising allowing two copies of the mature polypeptide to bond to form a mature multimeric protein.

- [0372] EXAMPLE 68 [[43.]] The method of ~~conclusion~~ EXAMPLE 66 [[41]] wherein the multimeric protein is an antibody or a Fab fragment or a derivative of either the antibody or the Fab fragment.
- [0373] EXAMPLE 69 [[44.]] A vector encoding an artificial preproprotein, comprising: a nucleotide sequence necessary for replication of the vector nucleotides and proteins and the artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] inserted into the vector.
- [0374] EXAMPLE 70 [[45.]] The vector of ~~conclusion~~ EXAMPLE 69 [[44]] that is a plasmid or a viral vector.
- [0375] EXAMPLE 71 [[46.]] The vector of ~~conclusion~~ EXAMPLE 69 [[44]] that is capable of being reproduced in a microorganism.
- [0376] EXAMPLE 72 [[47.]] A transiently transformed cell, comprising: a vector encoding an artificial preproprotein, comprising; a nucleotide sequence necessary for replication of the vector nucleotides and for expression of proteins; an artificial polynucleotide encoding an artificial preproprotein of ~~claim~~ EXAMPLE 39 [[14]] inserted into the vector; a promoter capable of directing expression of the artificial preproprotein; and the artificial preproprotein encoded by the artificial polynucleotide.
- [0377] EXAMPLE 73 [[48.]] The cell of ~~conclusion~~ EXAMPLE 72 [[47]] wherein the artificial preproprotein comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody, but the first peptide is different from the second peptide.
- [0378] EXAMPLE 74 [[49.]] The cell of ~~conclusion~~ EXAMPLE 72 [[47]], the cell further comprising a mature multimeric protein made from two copies of the artificial preproprotein.
- [0379] EXAMPLE 75 [[50.]] An organism comprising a plurality of cells according to ~~conclusion~~ EXAMPLE 72 [[47]].

- [0380] EXAMPLE 76 [[51.]] A plant, an animal, a fungus, or an algae organism according to ~~conclusion~~ EXAMPLE 74 [[49]] or 75 [[50]] wherein the organism is a plant, an animal a fungus or an algae.
- [0381] EXAMPLE 77 [[52.]] A plant cell, an animal cell, a fungus cell, an algae cell or a single celled organism according to ~~conclusion~~ EXAMPLE 72 [[47]].
- [0382] EXAMPLE 78 [[53.]] An organism comprising at least one cell according to ~~conclusion~~ EXAMPLE 72 [[47]] wherein the multimeric protein is secreted into the interstitial spaces or fluids of the organism.
- [0383] EXAMPLE 79 [[54.]] An organism according to ~~conclusion~~ EXAMPLE 74 [[49]] wherein the multimeric protein is secreted into the circulatory or ~~excretatory~~ excretory system of the organism.
- [0384] EXAMPLE 80 [[55.]] A transgenic cell, comprising: an artificial polynucleotide of ~~conclusion~~ EXAMPLE 39 [[14]] stably incorporated onto a chromosome, optionally a promoter capable of directing expression of the artificial preproprotein; and the artificial preproprotein encoded by the artificial polynucleotide.
- [0385] EXAMPLE 81 [[56.]] The cell of ~~conclusion~~ EXAMPLE 80 [[55]] wherein The artificial preproprotein comprises an antibody light chain peptide and an antibody heavy chain peptide, wherein the first peptide is either a heavy chain of the antibody or a light chain of the antibody, and wherein the second peptide is either a heavy chain of the antibody or a light chain of the antibody, but the first peptide is different from the second peptide.
- [0386] EXAMPLE 82 [[57.]] An organism comprising the cell of ~~conclusion~~ EXAMPLE 80 [[55]], the cell further comprising a mature multimeric protein made from two copies of the artificial preproprotein.
- [0387] EXAMPLE 83 [[58.]] An organism comprising a plurality of cells according to ~~conclusion~~ EXAMPLE 82 [[57]].
- [0388] EXAMPLE 84 [[59.]] A plant, an animal, a fungus, or an algae organism according to ~~conclusion~~ EXAMPLE 82 [[57]] or 83 [[58]] wherein the organism is a plant, an animal a fungus or an algae.

- [0389] EXAMPLE 85 [[60.]] A plant cell, an animal cell, a fungus cell, an algae cell or a single celled organism according to ~~conclusion~~ EXAMPLE 80 [[55]].
- [0390] EXAMPLE 86 [[61.]] An organism comprising at least one cell according to ~~conclusion~~ EXAMPLE [[55]] wherein the multimeric protein is secreted into the interstitial spaces or body fluids of the organism.
- [0391] EXAMPLE 87 [[62.]] An organism according to ~~conclusion~~ EXAMPLE 74 [[49]] wherein the multimeric protein is secreted into the circulatory or excretory system of the organism.
- [0392] EXAMPLE 88 [[63.]] A transgenic or transiently transformed organism containing or incorporating the artificial preproprotein of ~~conclusion~~ EXAMPLE 26 [[1]].
- [0393] EXAMPLE 89 [[64.]] A transgenic or transiently transformed plant, comprising plant cells containing an artificial polynucleotide sequence encoding an artificial preproprotein that artificial preproprotein comprises a) a signal peptide sequence, b) an immunoglobulin heavy chain or light chain peptide, c) a propeptide, and d) an immunoglobulin heavy chain or light chain peptide, wherein the heavy chain can be in either the b or the d position on the preproprotein, and the light chain will be on the other position, wherein The artificial preproprotein contains a signal peptide sequence signal peptide sequence forming a secretion signal; and containing immunoglobulin molecules encoded by said artificial polynucleotide sequence, wherein said signal peptide sequence signal peptide sequence is cleaved from said artificial preproprotein by proteolytic processing, and wherein said propeptide is cleaved from the heavy chain and the light chain following proper folding of the remaining polypeptide.
- [0394] EXAMPLE 90 [[65.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]] wherein the signal peptide sequences is a heterologous signal peptide sequence.
- [0395] EXAMPLE 91 [[66.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]] wherein the polynucleotide sequence encodes a mammalian immunoglobulin.
- [0396] EXAMPLE 92 [[67.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]] wherein the immunoglobulin is an immunoglobulin superfamily molecule.

[0397] EXAMPLE 93 [[68.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]] that is a dicotyledonous plant.

[0398] EXAMPLE 94 [[69.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]] that is a monocotyledonous plant (corn etc.).

[0399] EXAMPLE 95 [[70.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], that is a Nicotiana plant.

[0400] EXAMPLE 96 [[71.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein said polynucleotide sequence encoding the preproprotein is present on a single vector.

[0401] EXAMPLE 97 [[72.]] A method for making a transgenic plant capable of producing immunoglobulin molecules, comprising: (a) introducing into the genome of a member of a plant species an artificial polynucleotide sequence encoding a preproprotein that preproprotein comprises (i) a signal peptide sequence, (ii) an immunoglobulin heavy chain or light chain peptide, (iii) a propeptide, and (iv) an immunoglobulin heavy chain or light chain peptide, wherein the heavy chain can be in either the b or the d position on the preproprotein, and the light chain will be on the other position; and (b) allowing stable transformation to occur to produce a transformant.

[0402] EXAMPLE 98 [[73.]] The method of ~~conclusion~~ EXAMPLE 97 [[72]], wherein the signal peptide sequence is a heterologous signal peptide sequence.

[0403] EXAMPLE 99 [[74.]] The method of ~~conclusion~~ EXAMPLE 97 [[72]], wherein said first and second nucleotide sequences are introduced via the same vector.

[0404] EXAMPLE 100 [[75.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein at least some of said immunoglobulin molecules are present within the cell wall of said plant cells.

[0405] EXAMPLE 101 [[76.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein said immunoglobulin molecules are trafficked through the golgi of said plant cells.

[0406] EXAMPLE 102 [[77.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein said immunoglobulin molecules are selected from the group consisting of IgA, IgD, IgE, IgG, or IgM isotypes.

- [0407] EXAMPLE 103 [[78.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein said immunoglobulin molecules comprise the IgG isotype.
- [0408] EXAMPLE 104 [[79.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein said immunoglobulin molecules comprise the IgA isotype.
- [0409] EXAMPLE 105 [[80.]] The transgenic plant of ~~conclusion~~ EXAMPLE 89 [[64]] wherein The artificial preproprotein further comprises a promoter directing expression of said artificial polynucleotide.
- [0410] EXAMPLE 106 [[81.]] The plant of ~~conclusion~~ EXAMPLE 89 [[64]], wherein substantially all of the heavy- and light-chain peptides are assembled to form immunoglobulin molecules within said plant cell.
- [0411] EXAMPLE 107 [[82.]] The transgenic plant of ~~conclusion~~ EXAMPLE 105 [[80]] the promoter is a constitutive promoter.
- [0412] EXAMPLE 108 [[83.]] An artificial proprotein, comprising three peptide sequences: a first peptide sequence of interest; a propeptide sequence attached to the c-terminus of the first peptide sequence of interest; and a second peptide of interest attached to the c-terminus of the propeptide sequence.
- [0413] EXAMPLE 109 [[84.]] The artificial proprotein of ~~conclusion~~ EXAMPLE 108 [[83]] further comprising a signal peptide sequence attached to the N-terminus of the first peptide sequence of interest.
- [0414] EXAMPLE 110 [[85.]] A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of: transforming said single host cell with a single DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain, a propeptide and at least the variable domain of the immunoglobulin light chain, and expressing said single DNA sequence so that said immunoglobulin heavy and light chains are produced as a single propeptide molecule in said transformed single host cell.
- [0415] EXAMPLE 111 [[86.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein said single DNA sequence is present in different vectors.

- [0416] EXAMPLE 112 [[87.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein said single DNA sequence is present in a single vector.
- [0417] EXAMPLE 113 [[88.]] A process according to ~~conclusion~~ EXAMPLE 112 [[87]] wherein the vector is a plasmid.
- [0418] EXAMPLE 114 [[89.]] The process according to ~~conclusion~~ EXAMPLE 113 [[88]] wherein the plasmid is pBR322 or a derivative thereof.
- [0419] EXAMPLE 115 [[90.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein the host cell is a bacterium or yeast.
- [0420] EXAMPLE 116 [[91]] The process according to ~~conclusion~~ EXAMPLE 115 [[90]] wherein the host cell is *E. coli* or *S. cerevisiae*.
- [0421] EXAMPLE 117 [[92.]] A process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein the immunoglobulin heavy and light chains are expressed in the host cell and secreted therefrom as an immunologically functional immunoglobulin molecule or immunoglobulin fragment.
- [0422] EXAMPLE 118 [[93.]] A process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein the immunoglobulin heavy and light chains are produced in insoluble form and are solubilized and allowed to refold in solution to form an immunologically functional immunoglobulin molecule or immunoglobulin fragment.
- [0423] EXAMPLE 119 [[94.]] A process according to ~~conclusion~~ EXAMPLE 110 [[85]] wherein the DNA sequence codes for the complete immunoglobulin heavy and light chains.
- [0424] EXAMPLE 120 [[95.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]], wherein said single DNA sequence further encodes at least one constant domain, wherein the constant domain is derived from the same source as the variable domain to which it is attached.
- [0425] EXAMPLE 121 [[96.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]], wherein said single DNA sequence further encodes at least one constant domain, wherein the constant domain is derived from a species or class different from that from which the variable domain to which it is attached is derived.

- [0426] EXAMPLE 122 [[97.]] The process according to ~~conclusion~~ EXAMPLE 110 [[85]], wherein said single DNA sequence is derived from one or more monoclonal antibody-producing hybridomas.
- [0427] EXAMPLE 123 [[98.]] A vector comprising a single DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least a variable domain of an immunoglobulin light chain wherein said single DNA sequence is located in said vector at a single insertion site.
- [0428] EXAMPLE 124 [[99.]] A vector according to ~~conclusion~~ EXAMPLE 123 [[98]] that is a plasmid.
- [0429] EXAMPLE 125 [[100.]] A host cell transformed with a vector according to ~~conclusion~~ EXAMPLE 123 [[98]].
- [0430] EXAMPLE 126 [[101.]] A transformed host cell comprising at least two vectors, at least one of said vectors comprising a single DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least the variable domain of an immunoglobulin light chain.
- [0431] EXAMPLE 127 [[102.]] The process of ~~conclusion~~ EXAMPLE 110 [[85]], wherein the host cell is a mammalian cell.
- [0432] EXAMPLE 128 [[103.]] The transformed host cell of ~~conclusion~~ EXAMPLE 126 [[101]] wherein the host cell is a mammalian cell.
- [0433] EXAMPLE 129 [[104.]] A method comprising: preparing a DNA sequence consisting essentially of DNA encoding an immunoglobulin consisting of an immunoglobulin heavy chain and light chain or Fab region, said immunoglobulin having specificity for a particular known antigen, wherein the DNA sequence incorporates an artificial polynucleotide encoding a proprotein which consists of at least a variable domain of an immunoglobulin heavy chain, a cleavable propeptide, and at least the variable domain of an immunoglobulin light chain; inserting the DNA sequence of step a) into a replicable expression vector operably linked to a suitable promoter; transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of step b); culturing the host cell; and recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen.

- [0434] EXAMPLE 130 [[105.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the heavy and light chain are the heavy and light chains of anti-CEA antibody.
- [0435] EXAMPLE 131 [[106.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the heavy chain is of the gamma family.
- [0436] EXAMPLE 132 [[107.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the light chain is of the kappa family].
- [0437] EXAMPLE 133 [[108.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the vector contains DNA encoding both a heavy chain and a light chain.
- [0438] EXAMPLE 134 [[109.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the host cell is *E. coli* or yeast.
- [0439] EXAMPLE 135 [[110.]] The method of ~~conclusion~~ EXAMPLE 134 [[104]] wherein the heavy chain and light chains or Fab region are deposited within the cells as insoluble particles.
- [0440] EXAMPLE 136 [[111.]] The method of ~~conclusion~~ EXAMPLE 134 [[104]] wherein the proprotein is deposited within the cells as insoluble particles.
- [0441] EXAMPLE 137 [[112.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the proprotein is recovered from the particles by cell lysis followed by solubilization in denaturant.
- [0442] EXAMPLE 138 [[113.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the proprotein is secreted into the medium.
- [0443] EXAMPLE 139 [[114.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] wherein the host cell is a gram negative bacterium and the proprotein is secreted into the periplasmic space of the host cell bacterium.
- [0444] EXAMPLE 140 [[115.]] The method of ~~conclusion~~ EXAMPLE 129 [[104]] further comprising recovering both heavy and light chain and reconstituting light chain and heavy chain to form an immunoglobulin having specific affinity for a particular known antigen.

[0445] EXAMPLE 141 [[116.]] The insoluble particles of heavy chain and light chains or Fab region produced by the method of ~~conclusion~~ EXAMPLE 129 [[104]].

[0446] EXAMPLE 142 [[117.]] A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising: expressing a single DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as a single proprotein molecule in said single host cell transformed with said single DNA sequence.

[0447] EXAMPLE 143 [[118.]] The process of ~~conclusion~~ EXAMPLE [[92]], further comprising the step of attaching the immunoglobulin molecule or immunoglobulin fragment to a label or drug.

[0448] EXAMPLE 144 [[119.]] The process of ~~conclusion~~ EXAMPLE 118 [[93]], further comprising the step of attaching the immunoglobulin molecule or immunoglobulin fragment to a label or drug.

[0449] EXAMPLE 145 [[120.]] The process of ~~conclusion~~ EXAMPLE 142 [[117]], further comprising the step of attaching the immunoglobulin molecule or immunoglobulin fragment to a label or drug.

[0450] EXAMPLE 146 [[121.]] A multimeric protein encoded by an artificial polynucleotide according to conclusion 14, the multimeric protein selected from the group consisting of hemoglobin ($\alpha_2\beta_2$), IL-12, TCR, MHC class II heterodimer ($\alpha\beta$), CD8 heterodimer ($\alpha\beta$), CD3 ($\epsilon\delta$), CD3 ($\epsilon\gamma$), CD22($\alpha\beta$), CD41(GPIIb CD61) Janus kinase(JAK), JAK and STAT (signal transducers and activators of transcription) heterodimers, IgM heavy chain with I chain, or VpreB and lambda 5 (I chain), Ig β and Ig α , Integrins , T-cell integrin LFA-1 ($\alpha_L\beta_2$), CD152(CTLA-4), IL-2 receptor(heterotrimer) IL-2R($\alpha\beta\gamma$ c), IL-15($\alpha\beta\gamma$), Rhematopoietin receptor family (IL-3R, GM-CSFR are a few), TNF- β (LT- α and LT- β), IL12R($\beta_1\beta_2$), IgM (H₂L₂) with transgenic J chain, IgA (H₂L₂) with transgenic J chain, MHC class I (α and β_2 -microglobulin), HLA-DM($\alpha\beta$),H-2M($\alpha\beta$), E. coli DNA polymerase III, insulin

receptor(IR) ($\alpha_2\beta_2$), IGF-1 receptor($\alpha_2\beta_2$), G proteins heterotrimers ($\alpha\beta\gamma$),adrenergic receptor, retinoic acid receptor (RAR) ($\alpha\beta$), oestrogen receptor($\alpha\beta$),myocyte enhancer factors 2 (MEF2) family, c-fos and JunD, yeast RNAPII Rpb3/Rpb11 heterodimer, calpain, importin alpha2/beta heterodimer, DNA-dependent protein kinase (DNA-PKcs, and Ku70 and Ku80), Ku70 and Ku80 heterodimer, Hepatopoietin (HPO) and HPO23 heterodimer, leukocyte function associated antigen-1 molecule (LFA-1) CD11a (alphaL) and CD18 (beta2) integrin subunit heterodimer, liver X receptor (LXR)/ retinoid X receptor (RXR) heterodimer, eukaryotic structural maintenance of chromosome (SMC) proteins, human mismatch repair (MMR) heterodimers, rBAT-b(0,+)AT heterodimer, retinoid X alpha (RXRalpha) and peroxisome proliferator-activated receptor alpha (PPARalpha) heterodimer, thyroid hormone receptor (TR)/RXR heterodimer, peroxisome proliferator activated receptor/RXR, Nurr1 orphan nuclear receptor/RXR heterodimer, calcineurin, Collapsin response mediator protein-2 and tubulin heterodimer, CD94/NKG2A heterodimer, IkappaB kinase complex, human immunodeficiency virus reverse transcriptase (RT) heterodimer, CD98 complex, B cell antigen receptor with the membrane-bound immunoglobulin molecule (mIg) and the Ig-alpha/Ig-beta heterodimer, class IA phosphoinositide 3-kinase, hypoxia inducible factor 1.

[0451] EXAMPLE 147 [[122.]] The transgenic plant of ~~conclusion~~ EXAMPLE [[80]] the promoter is an inducible promoter.

[0452] EXAMPLE 148 [[123.]] A multimeric protein, comprising first and second peptides, the first peptide comprising a non-native amino acid pair at the P1 and P2 positions of the carboxy terminus.

[0453] EXAMPLE 149 [[124.]] A multimeric protein according to ~~conclusion~~ EXAMPLE 26 [[1]] wherein the P2 position is occupied by Lys, Pro, or Arg.

[0454] EXAMPLE 150 [[125.]] A multimeric protein according to ~~conclusion~~ EXAMPLE 26 [[1]] wherein the P1 position is occupied by Lys, Pro, or Arg.

[0455] EXAMPLE 151 [[126.]] A multimeric protein derived from a multimeric protein, comprising a first and second peptides, the first peptide comprising a non-native amino acid pair at the P1 and P2 positions of the carboxy terminus.